



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b>  <b>A61K 47/48</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 99/04822</b>  <b>(43) International Publication Date:</b> 4 February 1999 (04.02.99)
<b>(21) International Application Number:</b> PCT/HU98/00066  <b>(22) International Filing Date:</b> 22 July 1998 (22.07.98)  <b>(30) Priority Data:</b> P 97 01293                      25 July 1997 (25.07.97)                      HU  <b>(71) Applicant (for all designated States except US):</b> CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT. [HU/HU]; Tó u. 1-5, H-1045 Budapest (HU).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LEDNICZKY, László [HU/HU]; Üllő út 66/b, H-1082 Budapest (HU). SERES, István [HU/HU]; Frangepán u. 57, H-1044 Budapest (HU).  <b>(74) Common Representative:</b> CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT.; Iparjog, Tó u. 1-5, H-1045 Budapest (HU).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished          upon receipt of that report.</i>
<b>(54) Title:</b> NEW SALTS WITH BENEFICIAL ORGANOLEPTIC PROPERTIES  <b>(57) Abstract</b>  The invention relates to new salts of known drugs which have pleasant taste.		

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### New salts with beneficial organoleptic properties

The subject of the invention are compounds of the general formula (I) and their solvates that have organoleptically beneficial properties, pharmaceutical  
5 preparations containing the above mentioned compounds and/or their solvates, as well as a preparation of compounds of the general formula (I).

The disagreeable, bitter taste occurring during or right after oral administration is typical to the wide range of drug substances. These include various active ingredients such as drotaverin, prenoxidiazine, azithromycin, cimetidine,  
10 ciprofloxacin, erythromycin, fluoxetine, clarithromycin and ranitidine.

The bitter taste of a drug substance that is made up in form of fluid suspension can be observed during drinking the suspension or right after swallowing it. Therewith the bitter taste of a preparation that contains a bitter active ingredient can be sensed during the administration only if this bitter agent – due to keeping it in mouth for  
15 too long, chewing it accidentally or releasing in any other way – gets into contact with gustatory (taste) buds.

Generally, among routes of administration for several drug substances the oral dosage form is favored because it allows a simple and cheap dosage. However, it should often be considered, how cooperating patients are when they must take a  
20 tablet, capsule or suspension. Patients have numerous reasons why they do not want or are not able to ingest preparations administered orally, including, for example, the repugnant appearance of a dose form, its too large size, bad taste, or simply the fear that the unchewed drug can be stuck in the throat. Patient who have difficulty in taking oral dosage forms often retch, which really prevents oral administration.

25 This problem is very usual among kids, but happens to adults as well.

Therefore it is desirable to formulate pharmaceuticals in such a way by which the above mentioned problems can be eliminated. Generally coating and masking are useful to conceal the bitterness of drug substances. Accordingly, for example, chewable tablets had been developed, and they were increasingly accepted by  
30 patients, both children and others, having troubles with swallowing tablets or capsules as a whole. However, it happens very often that the drug substance has

such a bitter taste that it is really unbearable to chew it, and the bad taste or after-taste caused by that bitter ingredient prevents patients from accepting oral administration.

- 5 Therefore we aimed to find derivatives of drug substances that would not represent the bad taste or after-taste of drug substances, but therapeutically are still equal to the known forms of pharmaceutical active ingredients, mostly hydrochloride salts. We can surprisingly achieve our aim not by coating or masking but by producing salts or salt-solvates of drug substances formed with a sweetener, and then use  
10 them as active ingredients, or as a proportion of active ingredients, for pharmaceutical preparations.

We use the term of drug substance for the active ingredients of any human or animal drugs, whose organoleptic properties, especially taste and after-taste, are unpleasant for patients or certain groups of patients or for animals.

- 15 Sweeteners are defined here as every natural or synthetic sweetener that is used to sweeten human food or animal feed, and is known from literature at the time of filing of this patent application. Useful sweeteners are, for example, saccharin, acesulpham, aspartame, alitam, cyclohexylamino-sulphonic acid, glycirrizine acid and similar compounds.

- 20 Although we use the term of drug substance mainly for the above listed compounds, we do not exclude any other compounds that have unpleasant organoleptic properties.

- The drug substances from which the new derivatives of the general formula (I) can be prepared include, but are not limited to the following: drotaverin, prenoxdiazine,  
25 selegiline, drug substances with phentiazin structure, ciprofloxacin, fluoxetine, enalapril, clopidogrel, irbesartan, azithromycin, erythromycin, clarithromycin, cimetidine and ranitidine.

- The new compounds of the general formula (I) show the same qualitative therapeutical profile as the starting known pharmaceutically active ingredients and  
30 its known salts. For example as it is known the spasmolytic drotaverin and its hydrochloride are inhibitors of phosphodiesterase IV isoenzyme (PDE-IV) (EP-

0664127A2). The new drotaverin salts and their solvates represented by the general formula (I) are selective PDE-IV inhibitors as well:

	Compound	Human U937 (cell line) PDE-IV enzyme inhibition IC <sub>50</sub>
5	drotaverin hydrochloride	$4.7 \cdot 10^{-6}$ mol
	drotaverin cyclamate (Example 2)	$1 \cdot 10^{-6}$ mol
10	drotaverin saccharimide (Example 1)	$3.8 \cdot 10^{-6}$ mol

#### ASSAY:

15 Cyclic nucleotide phosphodiesterase activity is measured by a two-step procedure.

The standard assay mixture contains: 30µl of PDE IV enzyme,

20 µl of test compound or its solvent,

20µl of [<sup>3</sup>H]cAMP substrate (220000 dpm)

30 µl of 40 mM Tris buffer (pH=7.6)

20 containing 2.5 mM MgSO<sub>4</sub>.

The reaction is initiated by addition of the substrate.

Samples are incubated at 30 °C for 30 min. and the reaction is stopped by boiling the assay tubes for 2 min.

After cooling the tubes, 50µl of Crotalux atrox (0.5 mg/ml dest. water) is added and

25 the samples are incubated and shaken for 30 min at 37°C.

The nonreacted cAMP is removed by chromatography on Dowex 1x8 (Cl-form):

1 ml of Dowex is added to the sample and after vortex-mixing the resin is left to settle for 60 min. at room temperature. The mixture of 500 µl supernatant and 5 ml of liquid scintillation cocktail is measured to determine the amount of formed <sup>3</sup>H

30 adenosine.

**RESULTS CALCULATION:**

$$\text{inhibition\%} = 100 - \frac{I - C}{T - C}$$

5

I : enzyme activity in the presence of inhibitor

C : control (0 time)

T : total enzyme activity

IC<sub>50</sub> values were calculated by using of Medusa Version 1.4.

10

Furthermore in Figures 1 to 7 it is demonstrated that the pharmacological profiles are the same in case of drotaverin salts of the general formula (I) and the known drotaverin hydrochloride.

15 **Figure 1**

The spontaneous tracheal tone relaxant effect of two drotaverine salts was tested. Both salts concentration-dependently relaxed the tracheal tone. As it can be seen in Figure 1 there is no significant difference between the two salts in the respect of efficacy.

20

**Figure 2**

The histamine precontracted tracheal tone relaxant effect of the two drotaverine salts were tested. Both salts concentration-dependently relaxed the histamine induced tracheal contracture. As it can be seen in Figure 2 there is no significant

25

difference between the two salts in the respect of efficacy.

**Figure 3**

The inhibitory effect of the two drotaverine salts was tested on allergen (ovalbumin) induced tracheal contraction on isolated tracheal preparation derived from

30 ovalbumin presensitized guinea pigs. The area under the ovalbumin induced contraction curve was calculated (AUC) and its percentage decrease was used for

the characterisation of drug effect. Both salts concentration-dependently decreased the allergen response. There was not significant difference between the two salts in this respect.

5 **Figure 4**

The in vivo broncholytic effect of the two drotaverine salts were tested on allergen (ovalbumin) induced bronchoconstriction in allergen (ovalbumin) presensitized guinea pigs after intraduodenal administration. Both drotaverine salts shows dose-dependent broncholytic effect. There is no significant difference between the two salts in the respect of broncolitic effect.

**Figure 5**

The time duration of the broncholytic effect of the equimolar dose ( $\sim$ ED<sub>50</sub> dose) of the two drotaverine salts were tested on allergen (ovalbumin) induced bronchoconstriction test. Both salts have long-lasting broncholytic effect. The difference between the two time curves is not relevant so the pharmacological effect of the two salts are practically identical.

**Figure 6**

20 The in vivo broncholytic effect of the two drotaverine salts were tested on histamine induced bronchoconstriction test in guinea pigs after intraduodenal administration. Both drotaverine salts shows dose-dependent broncholytic effect. There is no significant difference between the two salts in the respect of broncolitic effect.

25 **Figure 7**

The allergen (ovalbumin) presensitized animals were treated by the equimolar doses of drotaverine salts for seven days (single p.o. dose/day). On the 8th day half of the animals of each salt treated group were treated by vehicle and 30 min. later the bronchoconstriction was evoked by the i.v. injection of allergen (ovalbumin). Both salts have significant broncholytic effect even 24 hours after the last treatment. There is no significant difference between the two salts in the respect of efficacy.

The other half of each salt treated group was treated again by the adequate salt and 30 min. later the bronch constriction was evoked by the i.v. injection of allergen. The acute broncholytic effect following subchronic treatment of both salts was higher as was expected on the basis of acute tests (see Figure 4). There is no  
5 significant difference between the two salts in the respect of efficacy.

Consequently the above new drotaverin salts and their solvates showing pleasant sweet taste are of great use in pharmaceuticals such as spasmolytic agents, antidepressive agents, tranquilizing agents, antidemential agents, antiinflammatory  
10 agents, antiallergic agents, antiasthmatic agents, liver-protecting agents, diuretic agents, etc., and also in medicaments for the prevention and therapy of various diseases including distortions of the central nervous system such as depression and dementia as well as others such as inflammation, allergic diseases, asthma, liver diseases and kidney diseases.

15

Compounds of the general formula (I) can be prepared by the reaction of the positive charged form (cation) of a drug substance with the negative charged form (anion) of a sweetener, using methods known per se. The above reaction is advantageously carried out in a solvent, and the compounds with general formula (I)  
20 are obtained and purified using common techniques.

The used drug substances and the sweeteners are commercial products.

Pharmaceutical preparations can be produced from compounds of the general formula (I) by common formulation techniques and using accepted fillers, diluents, lubricants, binding agents, pigments and stabilizing agents.

25 It should be noted that the compounds of the general formula (I) can show unobvious advantages in the field of bioavailability and/or formulation technology. We describe further details for our invention by the following examples, without limiting our claims to these examples.

30



**Example 1**

A 40°C solution of 20 g drotaverin base in 20 cm<sup>3</sup> absolute ethanol was added to the solution of 9.02 g saccharimide in 60 cm<sup>3</sup> hot, absolute (anhydrous) ethanol. The solution undergoing crystallization was cooled slowly; when it reached 10°C, it was clarified and covered with alcohol; the obtained 28.2 g of crude drotaverin-saccharimide ethanolate was recrystallized from 96% alcohol of threefold volume, with a yield of 95%. The obtained crystals are light yellow, MP: 95-97°C.

It is proven by the data of elementary analyses and spectra (IR, NMR) that the resulting substance is the solvate – containing one mole ethanol – of the salt formed by the reaction of drotaverin and saccharimide.

The elementary analysis data calculated for the empirical formula of C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>8</sub>S.C<sub>2</sub>H<sub>5</sub>OH are: (calculated C%=63.24; H%=6.75, N%=4.47, S%=5.12; measured C%=63.59, H%=6.68, N%=4.37, S%=5.25)

Assignment:

**IR** (Bruker IFS28 KBr pellet) 3498 νOH ethanol; 3085, 3064 νCH(aromatic); 2978, 2933, 2882 νCH (aliphatic); 2788-2338 νNH<sup>+</sup>; 1654 νC=O; 1610, 1571, 1518 aromatic structure vibration; 1258, 1044 νC-O-C

<sup>1</sup>H NMR (Bruker DRX-400; 400 Mhz CDCl<sub>3</sub>) 7.79 m [2H] saccharin 4.7-H; 7.58 m [2H] saccharin 5.6-H 7.28 s [1H] 8-H, 6.95 d [1H] 2'-H J<sub>2,6</sub>=1.9; 6.82 dd [1H] 6'-H J<sub>5,6</sub>=8.2; 6.75 d 6'-H; 6.73 s [1H] 5-H; 4.49 s [2H] CH<sub>2</sub>; 4.17 q [2H] 6-OCH<sub>2</sub> J<sub>OCH<sub>2</sub>,CH<sub>3</sub></sub>=7.0; 4.09 m [2H] 3-H<sub>2</sub>; 4.00 q [6H] 7-OCH<sub>2</sub>, 3'-OCH<sub>2</sub>, 4'-OCH<sub>2</sub>; 3.72 q [2H] ethanol OCH<sub>2</sub>; 3.00 m [2H] 4-H<sub>2</sub>; 1.48 t [3H], 1.40 t [3H], 1.38 t [3H], 1.33 t [3H] CH<sub>3</sub>; 1.22 t [3H] ethanol CH<sub>3</sub>.

**Example 2**

21.6 g drotaverin-hydrochloride was dissolved in 40 cm<sup>3</sup> of 96%, hot alcohol and then a solution of 10.2 g sodium cyclamate in 25 cm<sup>3</sup> distilled water was added. By cooling the solution, drotaverin cyclamate salt was crystallized at 32°C; after further cooling, it was kept at 5°C to crystallize for two hours, and then clarified, covered and dried with 50% alcohol;

Weight: 14.4 g (Color: almost white)

The crude product was recrystallized from 96% alcohol of threefold volume, with a yield of 80%; the obtained product is almost white. MP: Melting begins at 158 °C and it is a long lasting process.

- 5 It is proven by the data of elementary analyses and spectra (IR, NMR) that the resulting substance is the salt formed by the reaction of drotaverin and cyclohexylamino-sulphonic acid.

Assignment:

IR (Bruker IFS28, KBr pellet) 3285  $\nu$ NH; 3093, 3056  $\nu$ CH (aromatic);  
10 2975, 2923, 2854  $\nu$ CH (aliphatic); 1661  $\nu$ C $\equiv$ N; 1603, 1562, 1518 aromatic structure vibration, 1278 1035  $\nu$ C-O-C

$^1$ H NMR (Bruker DRX-400; 400 Mhz CDCl<sub>3</sub>) 7.24 s [1H] 8-H; 6.94 d [1H] 2'-H  $J_{2,6}$ = 1.9; 6.82 dd [1H] 6'-H  $J_{5,6}$ =8.2; 6.77 d 6'-H; 6.73 s [1H] 5-H; 4.36 s [2H] CH<sub>2</sub>; 4.17 q [2H] 6-OCH<sub>2</sub>  $J_{\text{OCH}_2\text{CH}_3}$ =7.0; 4.09 q [2H] 7-OCH<sub>2</sub>  $J_{\text{OCH}_2\text{CH}_3}$ =7.0; 4.02  
15 m [2H] 3-H<sub>2</sub>; 4.03 q [2H], 3.99 q [2H], 3'-OCH<sub>2</sub>, 4'-OCH<sub>2</sub>  $J_{\text{OCH}_2\text{CH}_3}$ =7.0; 3.28 m [1H] cyclamate 1-H; 2.98 m [2H] 4-H<sub>2</sub>; 1.49 t [3H], 1.42 t [3H], 1.41 t [3H], 1.40 t [3H] CH<sub>3</sub>; 2.11 m [2-H] 1.68 m [2H] 1.55 m [1H], 1.4-1.05 m [5H] cyclamate 2,3,4,5,6-H<sub>2</sub>

If the product was crystallized from water-organic solvent mixture, a product  
20 containing 1 mole of water as hydrate can be separated. In case of this monohydrate of drotaverin cyclamate the  $^1$ HNMR spectrum is the same as in case of the water free salt but the IR spectrum is the following:

IR (Bruker IFS28, KBr pellet) 3285  $\nu$ NH; 3093, 3056  $\nu$ CH (aromatic); 2975, 2923, 2854  $\nu$ CH (aliphatic); 1646  $\nu$ C  $\equiv$  N; 1603, 1562, 1518 aromatic structure vibration,  
25 1278, 1035  $\nu$ C-O-C;  $\nu$ OH(H<sub>2</sub>O) 3477, 3441.

### Example 3

10.9 g prenordiazine-base and 5.55 g (each 0.03 mole) saccharimide was dissolved in 75 cm<sup>3</sup> ebullient anhydrous ethanol. The clear solution was subject to  
30 crystallization by cooling and mixing; the resultant crystals were drawn off and

covered with some ethyl alcohol. The crude product was subject to vacuum drying.  
Weight: 16.03 g (97.4%) MP: 131-132°C.

The obtained prenoxdiazine saccharimide salt was subject to crystallization using anhydrous alcohol of 5.2-fold volume with a yield of 96%; MP: 131-132°C.

5 Elementary analyses of  $C_{30}H_{32}N_4O_4S$ :

C%	H%	N%	S%
66.16	5.92	10.29	5.89
66.45	6.06	10.48	5.92

10

It is proven by the data of elementary analyses and spectra (IR, NMR) that the resulting substance is the salt obtained by the reaction of prenoxdiazine and saccharimide.

Assignment:

15 IR (Bruker IFS28 KBr pellet) 3064, 3035, 3013;  $\nu$ CH (aromatic); 2962, 2940, 2919, 2868  $\nu$ CH (aliphatic); 2766-2120  $\nu$ NH<sup>+</sup>; 1644 saccharin  $\nu$ C=O; 1583, 1525, 1495; aromatic structure vibration; 751, 716 monosubs. aromatic

<sup>1</sup>H NMR (Bruker DRX-400, 400 MHz, CDCl<sub>3</sub>), 7.79 m [2H] saccharin 4.7-H; 7.62 m [2H] saccharin 5.6-H; 7.3-7.15 m [10H] aromatic-H; 4.60 t [1H] CH, J<sub>CH,CH2</sub>=8.2; 3.55 t [2H] NCH<sub>2</sub> J<sub>NCH2,5-CH2</sub>=7.4; 3.44 m [4H] 3-CH<sub>2</sub> 5-CH<sub>2</sub>; 3.1 b m [4H] 2'6'-H<sub>2</sub>; 1.98 b [4H]; 1.65 b [2H] 3',4',5'-H<sub>2</sub>

20

#### Example 4

##### Dry syrup

25 The following components were mixed:

drotaverin cyclamate	10.0 g (Example 2)
sodium pyrosulfit	3.0 g
citric acid	3.0 g
Keltrol ®	5.0 g
30 Nipagin ® M	5.0 g
saccharose	10.0 g

mannit 5.0 g

flavoring material qu. sat.

This mixture mixed with drinking water ad 100 ml gave the liquid syrup form with total volume of 100 ml.

- 5 Examination of organoleptical properties of above composition showed that the characteristic bitter taste of drotaverin did not appear.

### Example 5

#### Ready to use suspension

- 10 The same components were mixed as in Example 4 but aqua dest. was added to the solid mixture and it was bottled.

Examination of organoleptical properties of above composition showed that the characteristic bitter taste of drotaverin did not appear.

### 15 Example 6

#### Tablet composition

150 g drotaverin saccharimide (Example 1)

5 g magnesium stearate

8 g talcum

- 20 50 g pregelatinized starch

10 g PVP

100 g lactose

90 g microcrystalline cellulose

- were mixed, granulated and compressed into tablets with total weight of 413 mg  
25 containing 150 mg of active substance.

Examination of organoleptical properties of above composition showed that the characteristic bitter taste of drotaverin did not appear.

**Claims**

1. Compounds of the general formula (I) - where  
A is a positive charged ion (cation) of a drug substance,  
5 B is a negative charged ion (anion) of sweetener - and their solvates having  
organoleptically beneficial properties.
2. Compounds of the general formula (I) and their solvates according to claim 1  
where  
10 A is as defined in claim  
X means compounds containing negative charged ion of the formula (1), (2),  
(3), (4), (5) or (6) and their solvates.
3. Compounds of the general formula (I) and their solvates according to claim 1 -  
15 where  
A is a positive charged ion of drotaverin, prenoxdiazine, selegiline,  
azithromycin, cimetidine, ciprofloxacin, clopidogrel, irbesartan,  
erythromycin, fluoxetine, ranitidine, clarithromycin, enalapril.
- 20 4. Salt of drotaverin formed by the anion of the formula (1) and its solvates.
5. Salt of drotaverin formed by the anion of the formula (2) and its solvates.
6. Salt of drotaverin formed by the anion of the formula (3) and its solvates.
- 25 7. Salt of drotaverin formed by the anion of the formula (4) and its solvates.
8. Salt of drotaverin formed by the anion of the formula (5) and its solvates.
- 30 9. Salt of drotaverin formed by the anion of the formula (6) and its solvates.

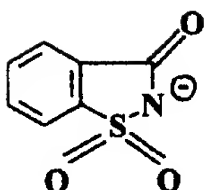
10. Salt of prenoxdiazine formed by the anion of the formula (1) and its solvates.
11. Salt of prenoxdiazine formed by the anion of the formula (2) and its solvates.
- 5 12. Salt of prenoxdiazine formed by the anion of the formula (3) and its solvates.
13. Salt of prenoxdiazine formed by the anion of the formula (4) and its solvates.
14. Salt of prenoxdiazine formed by the anion of the formula (5) and its solvates.
- 10 15. Salt of prenoxdiazine formed by the anion of the formula (6) and its solvates.
16. Pharmaceutical preparations characterized in that, they contain at least one compound of the general formula (I), - where A and X are as defined in claim 1  
15 - and/or its/their solvates.
17. Solid pharmaceutical preparations according to claim 6, characterized in that, they contain at least one compound of the general formula (I), - where A and X are as defined in claim 1 - and/or its/their solvates.
- 20 18. Liquid pharmaceutical preparations according to claim 16, characterized in that, they contain at least one compound of the general formula (I), - where A and X are as defined in claim 1 - and/or its/their solvates.
- 25 19. Process for the preparation of compounds of the general formula (I), characterized in that, a cation form (positive charged ion) of a drug substance is reacted with an anion form (negative charged ion) of a sweetener.
- 30 20. Procedure according to claim 17, characterized in that, the reaction is carried out in liquid medium.

21. An inhibitor for PDE-IV containing at least one of the compounds and/or their solvates according to claims 4 to 9 as therapeutically active component.
22. Use of at least one of the compounds and/or their solvates according to claims 4 to 9 for the preparation of pharmaceutical compositions for inhibiting PDE-IV enzyme.
23. Use of at least one of the compounds and/or their solvates according to claims 4 to 9 for the preparation of an antidepressive agent, a tranquilizer, an antimental agent, an antiinflammatory agent, an antiallergic agent, an antiasthmatic agent, a liver protecting agent or a diuretic agent.
24. A spasmolytic agent containing at least one of the compounds and/or their solvates according to claims 4 to 9 as therapeutically active component.
25. Use of at least one of the compounds and/or their solvates according to claims 4 to 9 for the preparation of spasmolytic pharmaceutical compositions.

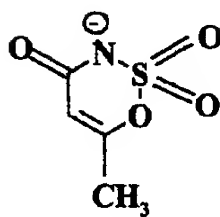
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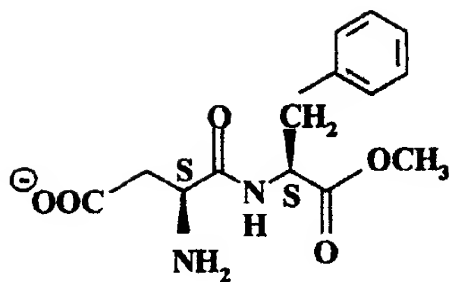
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(1)



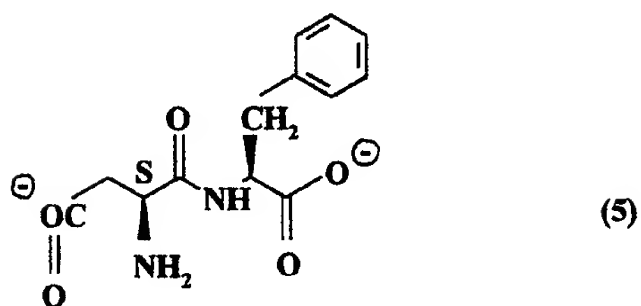
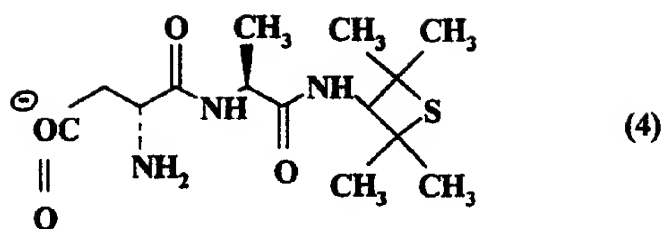
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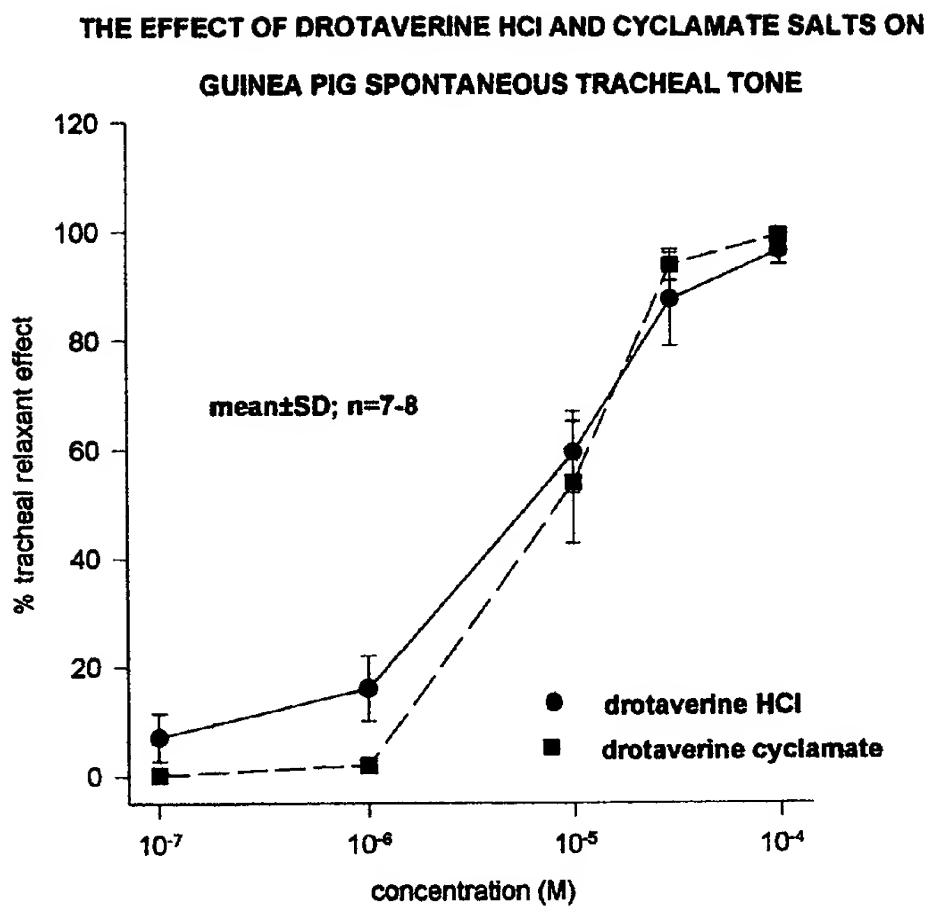


(3)



2/9

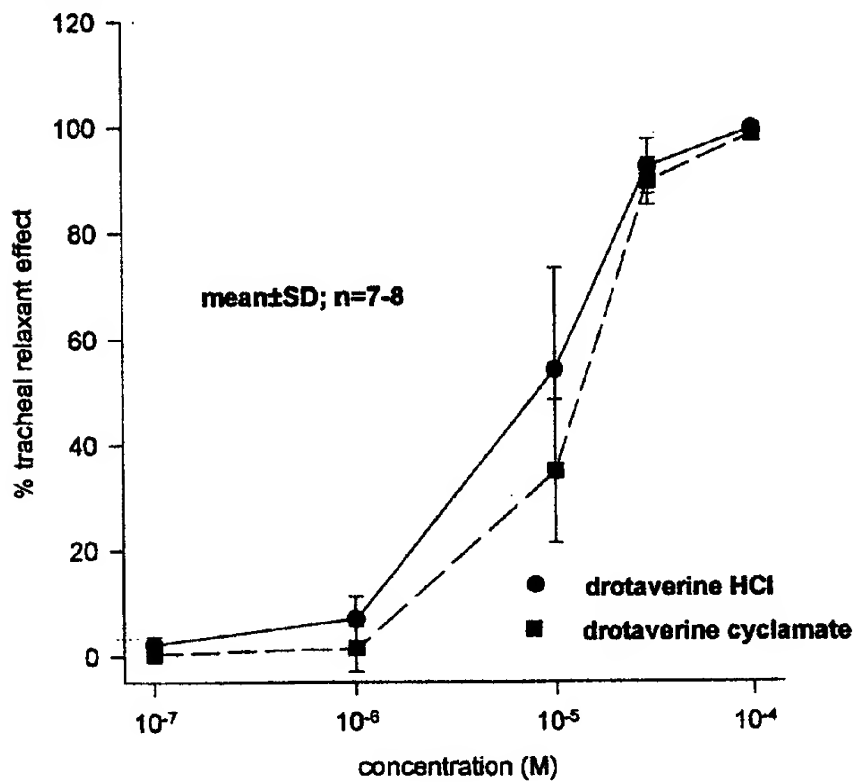


**Figure 1**

4/9

**Figure 2**

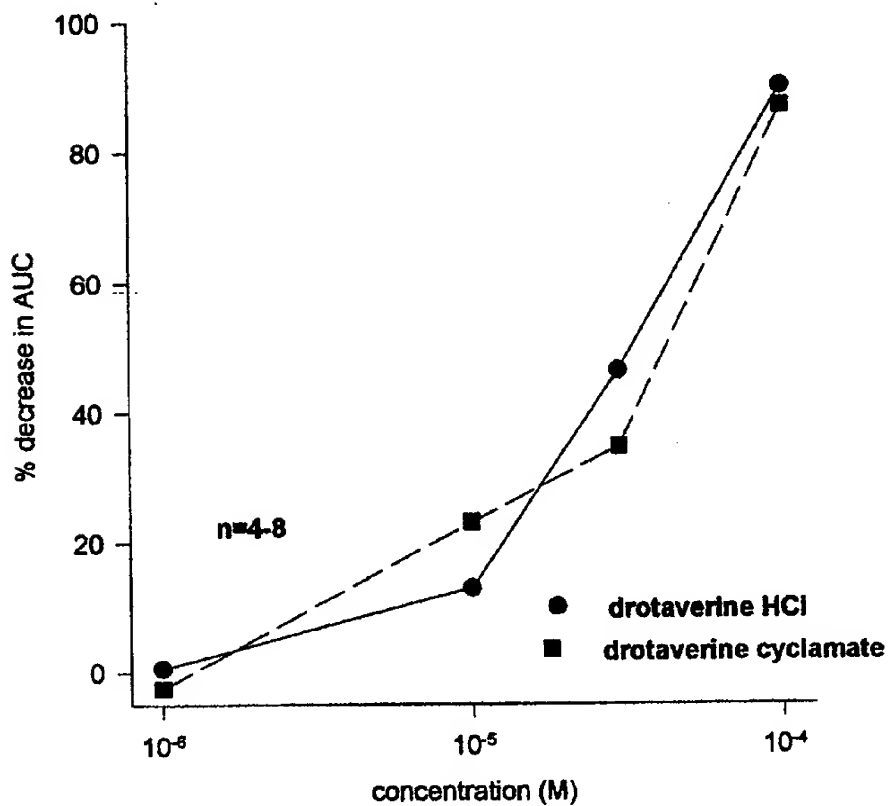
**THE EFFECT OF DROTAVERINE HCl AND CYCLAMATE SALTS ON  
GUINEA PIG HISTAMINE PRECONTRACTED TRACHEAL PREPARATIONS**



5/9

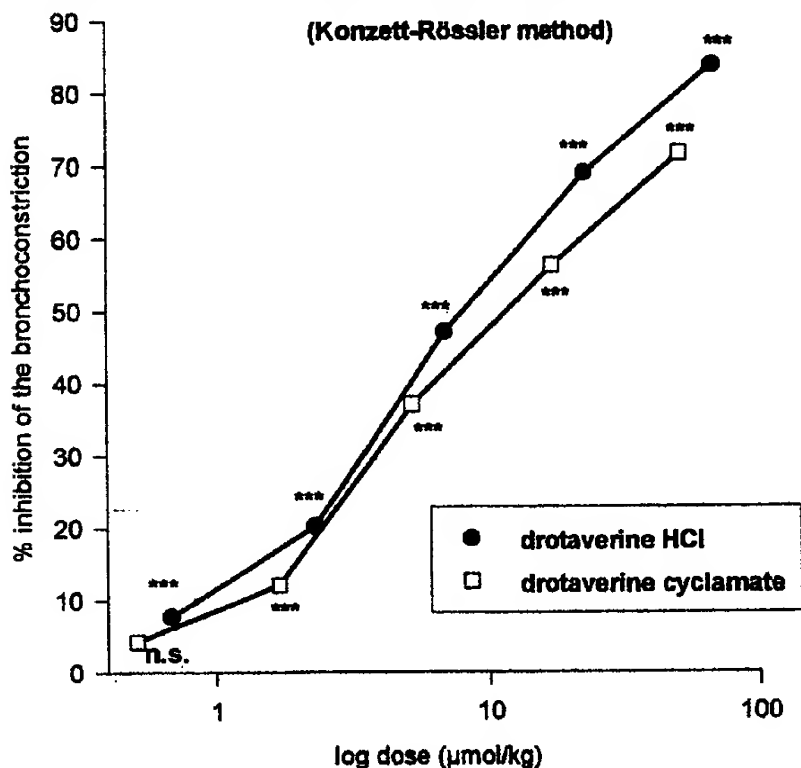
**Figure 3**

**THE EFFECT OF DROTAVERINE CYCLAMATE AND HCl SALTS ON  
OVALBUMIN INDUCED GUINEA PIG TRACHEAL CONTRACTION**



**Figure 4**

**THE EFFECT OF DROTAVERINE CYCLAMATE AND HCL SALTS ON  
ALLERGEN INDUCED BRONCHOCONSTRICTION IN ANAESTHETISED  
GUINEA PIGS 30 MIN AFTER INTRADUODENAL ADMINISTRATION**



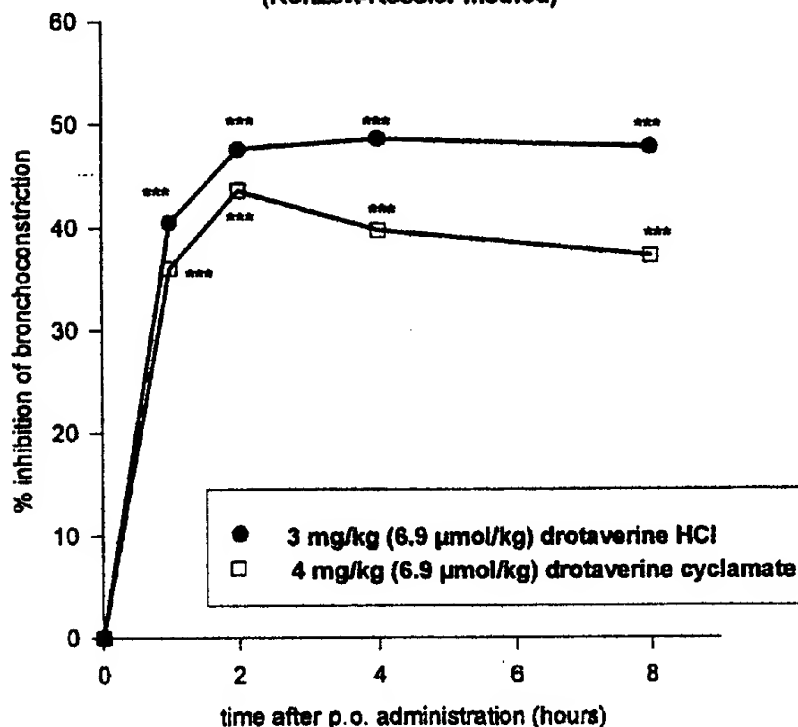
Statistical analysis by Student's unpaired t test, drug treated groups were compared to vehicle treated groups; n.s.=not significant

\*\*\*=p<0.001; n=3-4

7/9

**Figure 5**

THE TIME DEPENDENCE OF THE BRONCHOLITIC EFFECT OF  
DROTAVERINE HCl AND CYCLAMATE SALTS ON ALLEGEN EVOKED  
BRONCHOCONSTRICTION IN GUINEA PIG AFTER ORAL ADMINISTRATION  
(Konzett-Rössler method)



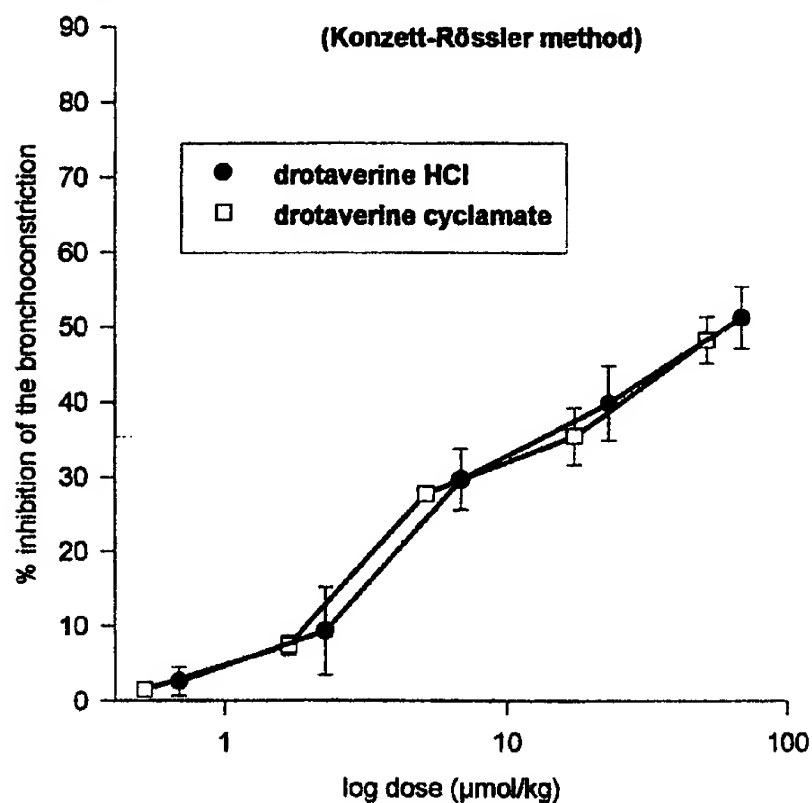
p.o. treatment in conscious state; statistical analysis by Student's unpaired t test  
test compound treated groups were compared to vehicle treated groups

\*\*\*p<0.001; n=4/time point

8/9

**Figure 6**

**THE EFFECT OF DROTAVERINE CYCLAMATE AND HCL SALTS ON  
HISTAMINE INDUCED BRONCHOCONSTRICTION IN ANAESTHETISED  
GUINEA PIGS 30 MIN AFTER INTRADUODENAL ADMINISTRATION**

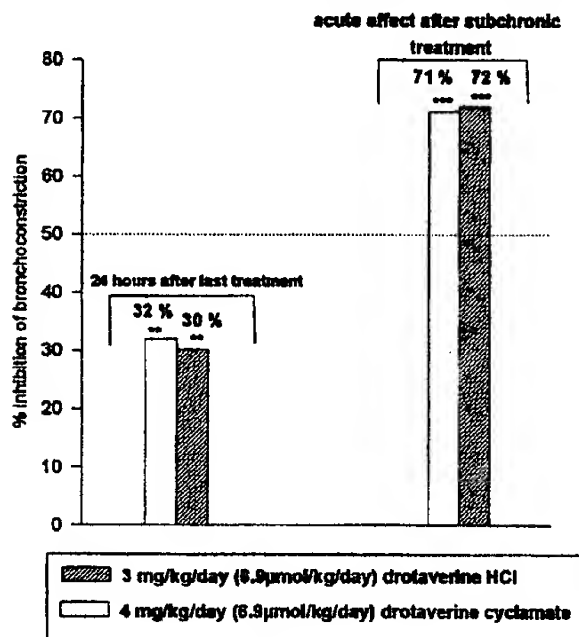


mean  $\pm$  SD; n=3-4

9/9

**Figure 7**

THE EFFECT OF SEVEN DAYS DROTAVERINE HCl OR CYCLAMATE SALT  
ORAL TREATMENT ON ALLERGEN INDUCED BRONCHOCONSTRICTION  
IN GUINEA PIGS 24 HOURS AFTER THE LAST TREATMENT  
AND ON THE ACUTE BRONCHOLITIC EFFECT OF THE TWO SALTS



Statistical analysis by Student's unpaired t test; drug treated groups were compared to vehicle treated groups; n=5; \*\*p<0.01; \*\*\*p<0.001 single dose/day treatment